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## Title Page

*Title:* Vascular and metabolic response to bevacizumab-containing regimens in two patients with colorectal liver metastases measured by dynamic contrast enhanced MRI and dynamic  $^{18}\text{F}$ -FDG PET.

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## **Conflict of Interest Page**

All authors have no conflicts of interest.

## Abstract

Early monitoring of response to treatment is one of the cornerstones of personalized treatment. As new and often expensive targeted therapies, which are tumoristatic rather than tumoricidal, become available, new demands are posed on response assessment. Bevacizumab, an antiangiogenic agent causing normalization of the tumor microvasculature, potentiates the effect of cytotoxic agents on colorectal liver metastases. It is known that assessment of glucose metabolism by (dynamic) positron emission tomography using [ $^{18}\text{F}$ ]-fluoro-2-deoxy-D-glucose ( $^{18}\text{F}$ -FDG PET) can be used as an early surrogate endpoint to determine treatment efficacy. Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) can be used to quantify functional tumor vasculature (permeability, vascular surface area). Here, we describe the response of colorectal liver metastases to cytotoxic regimens including bevacizumab using both  $^{18}\text{F}$ -FDG PET and DCE-MRI in 2 cases. In both cases, a large reduction in glucose metabolic rate and functional tumor vasculature is observed after three treatment cycles.

*Key-words:* colorectal carcinoma; DCE-MRI;  $^{18}\text{F}$ -FDG; PET; chemotherapy; therapy monitoring; bevacizumab

## Introduction

Progress in cytotoxic treatment of advanced colorectal cancer (CRC), has improved median survival from eight to more than 20 months.<sup>1</sup> For many tumor types it is known that they induce neoangiogenesis, leading to an intratumoral microcirculation that is characterized by tortuous microvessels with chaotic architecture and irregular, sluggish blood flow with unstable rheology. Angiogenesis inhibitors lead to normalization of tumor vasculature which may improve chemotherapy delivery.<sup>2</sup> In fact, the addition of bevacizumab to the standard first-line chemotherapy has improved response rate (34.8% to 44.8%), progression-free (6.2 to 10.6 months) and overall survival (15.6 to 20.3 months)<sup>3-6</sup> and this humanized monoclonal antibody against vascular endothelial growth factor A (VEGF-A) was approved for the treatment of metastatic colorectal cancer. Unfortunately, not all patients respond to systemic treatment. Early response prediction would help to identify patients, early in treatment, that most likely benefit from the addition of this monoclonal antibody therapy, increasing the beneficial effects and preventing side effects and costs due to ineffective treatments.

Capillary perfusion and permeability of the vessel wall can be measured in vivo by dynamic gadopentetate dimeglumine (Gd-DTPA) contrast-enhanced magnetic resonance imaging (DCE-MRI).<sup>7</sup> Pharmacokinetic analysis of DCE-MRI data using a 2-compartment model<sup>8, 9</sup> yields parameters for perfused capillaries including blood flow, permeability, and the total vessel surface area ( $K^{trans}$ : volume transfer constant,  $k_{ep}$ : compartmental rate constant, and  $v_e$ : volume of contrast extravascular extracellular space per unit volume of tissue). Assuming that vascularity, as reflected by these parameters, is modified by treatment by bevacizumab, it may be hypothesized that these parameters can be used for prediction of treatment response. The value of early monitoring of treatment response by DCE-MRI has been shown for rectal<sup>10</sup> and breast<sup>11-13</sup> cancer. Glucose metabolic activity can be assessed in vivo by positron emission tomography (PET) using the radionuclide labeled glucose-analogue [<sup>18</sup>F]-fluoro-2-deoxy-D-glucose (<sup>18</sup>F-FDG).<sup>14</sup> FDG uptake is increased in malignant

tumors. An adequate vascular supply is necessary for delivery of glucose to tumor cells as well as the presence of several membrane-bound glucose transport proteins and intracellular hexokinase for subsequent phosphorylation. FDG uptake can be quantified by pharmacokinetic compartment modeling<sup>14, 15</sup> of dynamic FDG-PET data leading to glucose metabolic rates ( $MR_{glc}$ ). The predictive value for early evaluation of treatment response, using changes in  $MR_{glc}$  during (chemo)therapy, has been shown in many tumor types including non-small cell lung carcinoma<sup>16</sup> and CRC<sup>17</sup>.

Previously we have shown that the vascularity parameter  $k_{ep}$ , reflecting the transfer rate of Gd-DTPA over the capillary membrane, was inversely correlated to FDG-uptake.<sup>18</sup> A positive correlation was observed between  $k_{ep}$  and histopathological vascular density and in surgically-removed colorectal liver metastases (CRLM). More recently, we described the influence of cytotoxic treatment on changes in vascular perfusion and permeability (DCE-MRI) and cell metabolism (dynamic  $^{18}F$ -FDG PET) showing no changes in Gd-DTPA transfer rates but high decreases in  $MR_{glc}$ , which was correlated to patient survival.<sup>19, 20</sup> Here we present findings of two patients with CRLM imaged by both DCE-MRI and  $^{18}F$ -FDG PET prior to and following 3 months of first-line chemotherapy including bevacizumab.

## Case reports

In patient A, a 57 year-old male (Karnofsky Performance Status Score: 90) with a history of myocardial infarction, a T<sub>3</sub>N<sub>2</sub>M<sub>x</sub> moderately differentiated adenocarcinoma of the sigmoid colon was resected. CT at follow-up showed two liver metastases, in Couinaud segment II/III (left) and VI (right), considered eligible for resection. However, during surgery it was concluded that these metastases were irresectable. The patient was treated by first-line FOLFOX4 therapy (bimonthly 2-h infusion of oxaliplatin (85 mg/m<sup>2</sup>) combined with weekly 2-h infusion of folinic acid (200 mg/m<sup>2</sup>) and 24-h continuous infusion of 5-fluorouracil (2600 mg/m<sup>2</sup>) combined with bevacizumab (10 mg/kg) 30-90-min infusion every 3 weeks.<sup>21</sup> Initial assessment after 3 treatment cycles by MRI showed stabilization of disease (28% reduction according to the response evaluation criteria in solid tumors (RECIST v1.0<sup>22</sup>)). Compared to baseline, the dynamic <sup>18</sup>F-FDG PET (performed 3 days after the last therapy day of the 3<sup>rd</sup> cycle as previously described<sup>20</sup>) showed a 80% reduction in MR<sub>glc</sub> of the lesions corresponding to a reduction in standardized uptake value (SUV, the activity concentration in the tumor corrected for injected activity and patient body weight) on the static images of 23%. The DCE-MRI performed the same day showed a clear decrease in K<sup>trans</sup> and k<sub>ep</sub> of 40% and 58% respectively (table 1, figure 1).

Due to polyneuropathy and therapy resistant diarrhea, oxaliplatin had to be stopped after 9 cycles. After 12 cycles in total, stable disease on MRI persisted according to the RECIST-criteria and treatment was stopped. Six days after the last therapeutic day, the MR<sub>glc</sub> and SUV remained at similarly reduced levels compared to baseline (reduction of 89% and 20%, respectively). The k<sub>ep</sub> however was only slightly lower than baseline and K<sup>trans</sup> had increased.

Follow-up 3 months after the end of the previous treatment scheme, progressive disease was observed, which did not respond to second-line therapy with irinotecan. The patient died 2 years after the start of chemotherapy, which is somewhat longer than the median overall survival known for this treatment scheme.<sup>3</sup>

Patient B, a 58-year old male (Karnofsky Performance Status Score: 90) with a history of prostate cancer treated by laparoscopic prostatectomy 55 months earlier, was diagnosed with a T<sub>3</sub>N<sub>2</sub>M<sub>1</sub> poorly differentiated adenocarcinoma in the sigmoid. A low-anterior resection with end colostomy was performed. Palliative chemotherapy was started for multiple synchronous CRLM with first-line capecitabine orally (1000 mg/m<sup>2</sup> twice daily on days 1–14), combined with infusion of oxaliplatin (130 mg/m<sup>2</sup> on day 1) and bevacizumab (7.5 mg/kg on day 1) plus cetuximab (400 mg/m<sup>2</sup> in week 1 of the first treatment cycle and 250 mg/m<sup>2</sup> weekly thereafter).<sup>23</sup> All cycles were administered every 3 weeks. To prevent serious peripheral sensory neurotoxicity, oxaliplatin was administered during a maximum of 6 cycles, after which the capecitabine dose was increased to 1250 mg/m<sup>2</sup> orally twice daily. Initial assessment after 3 cycles by MRI showed a partial response (82% reduction according to RECIST). Compared to baseline, the dynamic <sup>18</sup>F-FDG PET (performed the day after the last therapy day of the 3<sup>rd</sup> cycle) a 90% reduction in MR<sub>glc</sub> of the lesions was seen corresponding to a reduction in SUV on the static images of 24%. The DCE-MRI performed the same day showed a clear decrease in K<sup>trans</sup> and k<sub>ep</sub> of 93% (table 1, figure 2).

Follow-up after 9 cycles of chemotherapy by MRI showed a complete response according to RECIST. The dynamic <sup>18</sup>F-FDG PET (performed the day after the last therapy day of the 9<sup>th</sup> cycle) showed a further reduction of MR<sub>glc</sub> with 96% compared to baseline, the SUV remained stable at 22% below baseline (table 1). Unfortunately, the DCE-MRI performed that day could not be analyzed due to a human mistake in saving the images.

After 17 cycles this treatment regimen was discontinued due to the development of lung metastases and cetuximab-related skin toxicity. Less than 30% of patients on this treatment scheme have a progression-free survival of this duration.<sup>23</sup> After the 5<sup>th</sup> cycle of second-line treatment with 3-weekly irinotecan, treatment was switched to oxaliplatin combined with capecitabine due to a peritonitis carcinomatosis. Despite treatment the disease remained progressive and the patient died



21 months after the start of chemotherapy. His overall survival was comparable to the median survival of this treatment scheme (19.4 months).<sup>23</sup>

## Discussion

In this case series of 2 patients treated with bevacizumab-containing therapeutic regimens we saw a strong decrease in vessel perfusion and permeability as assessed by DCE-MRI. These results suggest that DCE-MRI can be used to assess tumor response to vascular targeting therapy. In contrast, in 23 other patients with CRLM treated with cytotoxic (non-targeting) chemotherapeutic agents, we saw similar responses in glucose metabolism, which were correlated with patient overall and progression-free survival.<sup>20</sup> However, in that study no changes in DCE-MRI parameters were observed.

To the best of our knowledge, this is the first report of clinical response monitoring of antiangiogenic treatment of CRLM with bevacizumab by DCE-MRI, excluding therapy with tyrosine kinase inhibitors. Wedam et al.<sup>24</sup> showed in 20 patients with inflammatory and locally advanced breast cancer that treatment with bevacizumab for 1 cycle followed by bevacizumab/doxorubicin/docetaxel for 6 cycles reduced vascular parameters quantified by DCE-MRI with Gd-DTPA. From baseline to the end of the first cycle (bevacizumab alone) they saw a decrease in  $k_{ep}$ ,  $K^{trans}$  and  $v_e$  of 58.0%, 49.4% and 20.4%, respectively. After 7 cycles in total, these decreased further, being 75.5%, 59.1% and 20.2% compared to baseline. However, they could not find a significant difference in any of the DCE-MRI parameters comparing clinical responders with nonresponders. Thukral et al.<sup>13</sup> followed 19 patients with inflammatory or locally advanced breast cancer treated with 1 cycle of bevacizumab alone followed by 6 cycles of bevacizumab added to chemotherapy using DCE-MRI with Gd-DTPA. The median values of  $K^{trans}$ ,  $k_{ep}$  and the integrated (180s) area under the concentration-time curve (IAUC<sub>180</sub>) showed significant decreases from baseline to cycle 1 of 34% ( $p=.003$ ), 15% ( $p<.001$ ) and 23% ( $p=.009$ ), respectively. Similarly, Baar et al.<sup>25</sup> recently showed that bevacizumab decreases tumor perfusion as measured by DCE-MRI. Forty-nine patients with inoperable breast cancer were randomized to either 2 cycles of neoadjuvant docetaxel weekly for 6 weeks or docetaxel/bevacizumab every other week for 16 weeks. DCE-MRI using Gd-DTPA was performed at baseline and after the first and second treatment cycle. All patients showed

a decrease in  $IAUC_{90}$  which was larger for patient using docetaxel/bevacizumab than patients treated with docetaxel alone ( $p=0.024$ ). This decrease was more profound after 2 than after 1 treatment cycle.

Therapy response assessment using DCE-MRI therefore shows variable results, depending on the treatment schedule used, contrast medium administered and analysis performed (heuristic or compartment analysis) and may even differ between different tumors. As these 2 cases are illustrative of treatment response assessment by DCE-MRI, larger trials should be performed to assess its true value and to determine the most useful parameter and optimal time-point for evaluation.

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## Tables

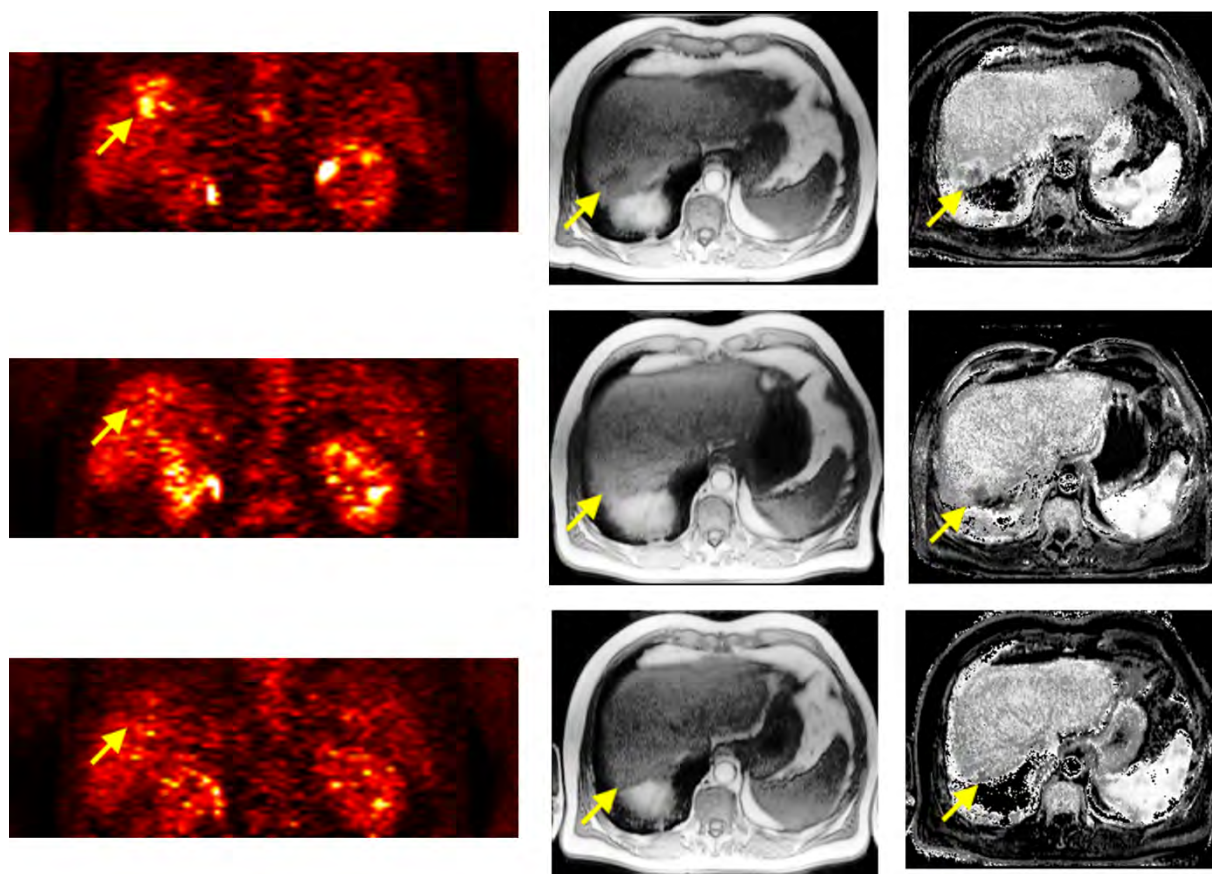
	<u>Baseline:</u>	<u>3 cycles:</u>	<u>Late:</u>
<b>Patient A:</b>			
<i>FDG-PET:</i>			
- MR <sub>glc</sub> [nmol/min/cm <sup>3</sup> ]	91.7	18.4 (-80%)	10.1 (-89%)
- SUV [g/cm <sup>3</sup> ]	5.3	4.1 (-23%)	4.2 (-20%)
<i>DCE-MRI:</i>			
- K <sup>trans</sup> [/s]	0.0156	0.0094 (-40%)	0.0183 (+17%)
- k <sub>ep</sub> [/s]	0.0304	0.0127 (-58%)	0.0295 (-3%)
<i>Survival:</i>			
- PFS [months]	9.1		
- OS [months]	26.8		
<b>Patient B:</b>			
<i>FDG-PET:</i>			
- MR <sub>glc</sub> [nmol/min/cm <sup>3</sup> ]	80.4	7.8 (-90%)	3.2 (-96%)
- SUV [g/cm <sup>3</sup> ]	4.3	3.2 (-24%)	3.4 (-22%)
<i>DCE-MRI:</i>			
- K <sup>trans</sup> [/s]	0.0895	0.0064 (-93%)	NA
- k <sub>ep</sub> [/s]	0.122	0.0086 (-93%)	NA
<i>Survival:</i>			
- PFS [months]	13.8		
- OS [months]	23.2		

**Table 1:** Responses in imaging parameters of the 2 patients described between baseline, after 3 treatment cycles and a late acquisition (12 cycles for patient A, 9 cycles for patient B). Relative changes compared to the baseline scan are displayed between brackets. DCE-MRI: dynamic gadopentetate dimeglumine contrast enhanced MRI; FDG-PET: [<sup>18</sup>F]-fluoro-2-deoxy-D-glucose positron emission tomography; k<sub>ep</sub>: compartmental rate constant; K<sup>trans</sup>: volume transfer constant;

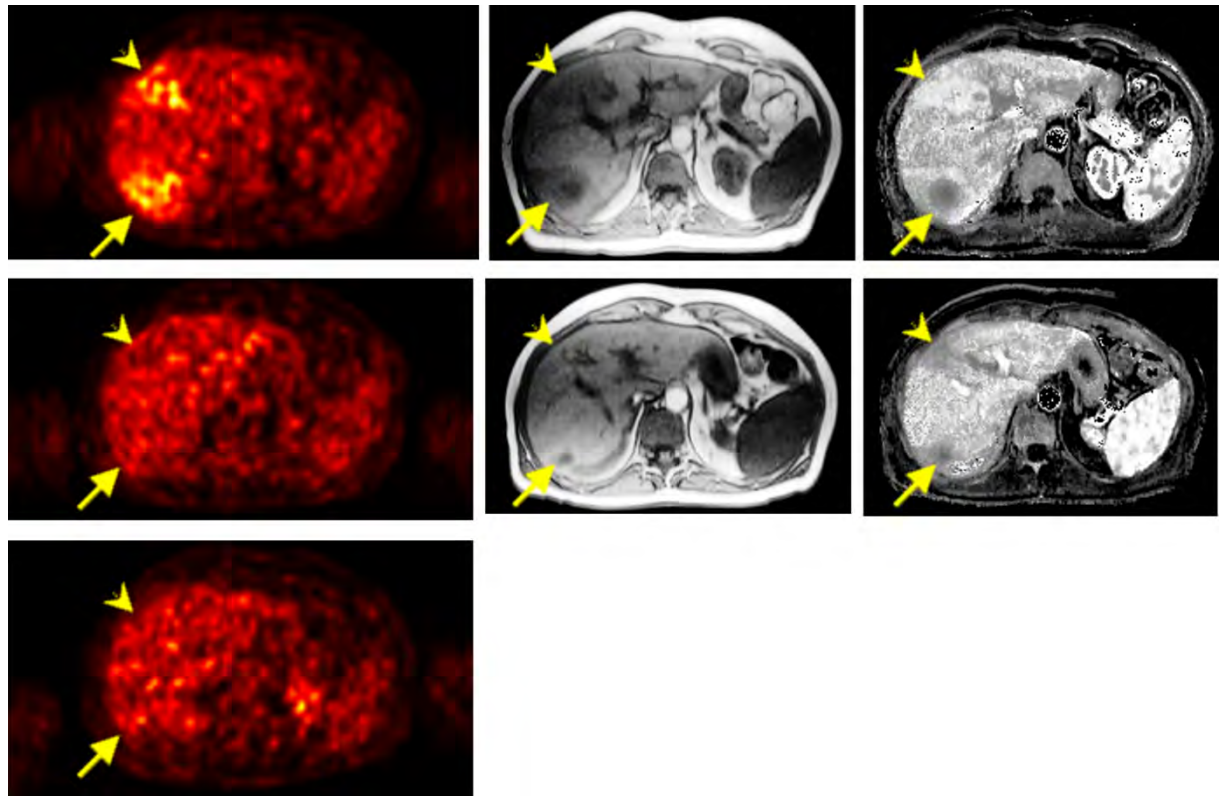
MR<sub>glc</sub>: glucose metabolic rate; NA: not available; OS: overall survival; PFS: progression-free survival;  
SUV: standardized uptake value (the activity concentration in the tumor corrected for injected activity and patient body weight).



## Figures



**Figure 1:** Patient A. Static [ $^{18}\text{F}$ ]-fluoro-2-deoxy-D-glucose positron emission tomography acquired 40-50 minutes after injection of the tracer (left panels). Enhanced T1 (middle panels) and parametric  $k_{\text{ep}}$  (right panels) DCE-MRI images. From top row (baseline) via middle row (after 1 treatment cycle) to lower row (after 12 cycles of therapy) it can be clearly seen that glucose metabolism as well as  $k_{\text{ep}}$  decrease in the lesion displayed (Couinaud segment VII (arrow)).



**Figure 1:** Patient B. Static [ $^{18}\text{F}$ ]-fluoro-2-deoxy-D-glucose positron emission tomography acquired 40-50 minutes after injection of the tracer (left panels). Enhanced T1 (middle panels) and parametric  $k_{ep}$  (right panels) DCE-MRI images. From top row (baseline) via middle row (after 1 treatment cycle) to lower row (after 9 cycles of therapy) it can be clearly seen that glucose metabolism as well as  $k_{ep}$  decrease in the 2 lesions displayed (Couinaud segments IVa (arrowhead) and VII (arrow)). Due to technical problems no MRI data was available for this patient after 9 cycles of therapy.

